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The Pennsylvania State University

The Graduate School

Department of Chemistry

Useful Syntheses of
Fluoroformates and 1-Alkenyl Carbonates

A Thesis in

Chemistry

by

Vu Anh Dang

Submitted in Partial Fulfillment
of the Requirements
for the Degree of

Doctor of Philosophy

December 1986

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Vu Anh Dang

ABSTRACT

Treatment of aldehydes (R_2CHCHO , **1**) with fluoroformates (FCO_2R' , **2**) and KF in DMSO (55–100 °C for 15–24 h) affords 1-alkenyl carbonates ($R_2C=CHOCO_2R'$, **3**) in 72–92% yield. In this process, the activated fluoride, acting as a base, deprotonates **1** to yield an enolate which is acylated rapidly by **2** to give **3** and KHF_2 . The reaction also can be performed in acetonitrile if 18-crown-6 is used as a catalyst. In this system, chloroformates may be substituted for **2** if an extra equivalent of KF is included in the reaction medium. In the acetonitrile procedure, the yields are as good and the conditions are milder, but 1-fluoroalkyl carbonates ($R_2CHCHF-OCO_2R'$, **4**) often are significant side products. The carbonates **4** equal **3** in yield when the reaction is performed without solvent; **4** is obtained as the sole product when the aldehyde contains no enolizable proton.

When 1-chloroalkyl carbonates ($R_2CH-CHClOCO_2R'$, **5**) are heated with KF/18-crown-6/MeCN, they fragment to **1** and **2** which recombine to give **3** in good yield. The chloroformate precursors to **5** are easily made by treatment of **1** with $COCl_2$ in the presence of a "naked chloride" catalyst using earlier methodology invented in this laboratory in collaboration with SNPE.

If the system is evacuated when **5** is reacted as above, the volatile **2** distills from the mixture as formed. Fluoroformates, previously unavailable by practical routes, which have been isolated by the

new method include *t*-butyl fluoroformate (84% yield, **6**), *t*-amyl fluoroformate (83%), and benzyl fluoroformate (60%). Other approaches to **2** are reported. The fluoroformate **6** could play a valuable role as a tBOC source in peptide synthesis.

Chloroformates react exothermically with DMSO. In contrast, fluoroformates are stable in DMSO below 100 °C. Thus, DMSO is an excellent solvent for the carboalkoxylation of carbohydrates and other polar nucleophiles with **2**. The carboalkoxylation studies included glucose, sucrose, cellulose, and polyvinyl alcohol (avg MW 14,000).

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EXPERIMENTAL SECTION

Melting points (mp) were determined in Kimax soft glass capillary tubes using a Thomas-Hoover "Uni-melt" Capillary Melting Point Apparatus, Model 6406 K, and are uncorrected.

Nuclear magnetic resonance (NMR) spectra were obtained on a Varian Model EM 360 or on a Bruker WP 200 Super Con Spectrometer. Chemical shifts are expressed in delta (δ) units with tetramethylsilane (TMS) as an internal standard. Coupling constants (J values) are given in Hertz (Hz) and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet). Infrared (IR) spectra were recorded on a Perkin Elmer 281B infrared spectrophotometer and were calibrated against the 1601.8 cm^{-1} band of polystyrene. Absorptions are given in cm^{-1} and are listed as very strong (vs), strong (s), medium (m), or weak (w). Mass spectral (MS) data were recorded at 70 eV on a Kratos MS-950 double-focusing high-resolution mass spectrometer or on a Finnigan 3200 CI quadrupole mass spectrometer equipped with a Finnigan 6000 computer.

Combustion analyses were performed by Mic-Anal Organic Microanalysis or Micro-Tech Laboratories.

Commercial anhydrous potassium fluoride (KF) and sodium fluoride (NaF) were dried in an oven at 170°C overnight before use. Vinyl chloroformate, isopropenyl chloroformate, 1-chloroethyl chloroformate

(ACE-Cl), and 1-chloroethyl ethyl carbonate were obtained as gifts from SNPE and were distilled before use. When used as solvents, dimethylformamide (DMF), methylene chloride, and acetonitrile, were gold label reagents obtained from Aldrich and were stored over Linde 4 Å molecular sieves. Other solvents and reagents were of the best commercial grade available and were utilized without purification unless specified. The deuterated NMR solvents contained 99–99.8% deuterium and were obtained from Diaprep, Inc. or Merck and Co.

Gas chromatography (GC) was performed in a Varian Model 920 Gas Chromatograph equipped with a thermal conductivity detector and a 5' x 1/4" 10% SP-2100 on Supelcoport, 80/100 mesh column. The carrier gas always was helium. Unless noted, chromatography columns were packed with 70–230 mesh Silica Gel 60 (Merck). Precoated (0.5 mm) Silica Gel GF₂₅₄ plates (Analtech, Inc.) were used for analytical and preparative thin layer chromatography (TLC).

All processes requiring anhydrous conditions were performed in oven-dried glassware (170 °C) cooled in a stream of dried N₂ (CaSO₄). The apparatus was designed to maintain a small positive pressure (bubble release) of dried N₂ during the reaction.

Chloromethyl Chloroformate. The unpublished procedure of Martz⁷⁵ was followed. Danger Phosgene: See reference 15 for precautions and procedures used here when working with phosgene. Phosgene (Matheson) (51.8 g, 0.053 mol) and PhCH₂N⁺(n-Bu)₃ Cl[−] (Aldrich) (10.7 g, 0.034 mol) were stirred at 0 °C in a 100 mL reactor fitted with a gas entry

Benzyl Fluoroformate (32) from Carbonyl Fluoride. Phosgene (18.0 mL, 0.26 mol) was added to a reaction flask (dry ice/acetone bath) containing NaF (25.0 g, 0.59 mol) and acetonitrile (7 mL) in sulfolane (25 g). The flask was topped by a dry ice/acetone condenser connected to a collector (0 °C) which contained benzyl alcohol (18.5 g, 0.17 mol) and dried KF (11.0 g, 0.19 mol) in 15 mL of ether. After 3 h of warming up to and stirring at room temperature, IR analysis of the slurry in the collector showed that no alcohol remained. Gases were removed by flushing with N₂ and the collected mixture then was filtered. The concentrated filtrate was vacuum distilled to give pure **32**; bp 60-61 °C at 3 mm, 21.7 g (83% yield); IR (CCl₄) 1830 cm⁻¹ (s); ¹H NMR (CCl₄) δ 7.42 (s, 5 H), 5.25 (s, 2 H).

A little AgCl precipitated when AgNO₃ in dilute HNO₃ was added to the precipitated KF-KHF₂ in water; 3 mol % vs alcohol.

In another study, phosgene (20.0 g, 0.29 mol) was reacted as above with KF (37.0 g, 0.64 mol) and 18-crown-6 (1.9 g, 0.0072 mol) in 40 mL of acetonitrile. The collector (at 0 °C) contained benzyl alcohol (8.70 g, 0.080 mol) and KF (5.0 g, 0.081 mol) in 10 mL of ether. After 1 h at room temperature, N₂ was flushed through the collector and the slurry in the collector then was filtered. The filtrate was vacuum distilled to give **32** in 87% yield (10.8 g).

t-Butyl Fluoroformate (10) from Carbonyl Fluoride. The first procedure described above was reproduced with phosgene (13 mL, 0.19 mol),

NaF (20.0 g, 0.476 mol), acetonitrile (5 mL), and sulfolane (20 mL) in the reaction flask and *t*-butanol (11.8 g, 0.159 mol), dried KF (10.0 g, 0.172 mol), and diglyme (distilled from KOH) (10 mL) in the collector. After 3.5 h at room temperature, the slurry in the collector was filtered to removed the KF and KHF_2 and the filtrate was distilled to isolate **10**; 16.0 g (84% distilled yield), 48–50 °C at 175 mm.

Adamantyl Fluoroformate (31) from Carbonyl Fluoride. The COF_2 formed from phosgene (9.50 g, 0.098 mol), NaF (10.0 g, 0.24 mol), acetonitrile (3 mL), and sulfolane (11 g) was passed into a collector kept at 0 °C which contained 1-adamantanol (10.0 g, 0.06 mol) and KF (4.0 g, 0.069 mol) in 30 mL of CH_2Cl_2 . After 3.5 h at room temperature, the slurry in the collector was flushed with N_2 and filtered. The filtrate was concentrated to give **31** as a white solid; mp 30–32 °C, 11.2 g (84% yield); IR (CCl_4) 1830 cm^{-1} (s); ^1H NMR (CCl_4) δ 2.18 (center of broad s, 9 H), 1.82 (center of broad s, 6 H).

Ethyl Fluoroformate (14) from Carbonyl Fluoride. The COF_2 obtained from a mixture of phosgene (14.0 g, 0.10 mol), NaF (12.5 g, 0.3 mol), acetonitrile (3 mL), and sulfolane (11 g) was passed into a collector maintained at -40 °C which contained ethanol (4.5 g, 0.098 mol), KF (5.5 g, 0.096 mol), and heptane (Aldrich) (20 mL). After 3.5 h (all EtOH converted to **14**), N_2 was flushed through the collector to remove volatile gases. The volatile liquid was separated from the KF and KHF_2 by vacuum evaporation into a -80 °C trap. The mixture of

heptane and fluoroformate then was distilled to give pure 14; bp 56-58 °C, 6.6 g (74% yield); IR (CCl₄) 1830 cm⁻¹ (s); ¹H NMR (CCl₄) δ 4.50 (q, 2 H, J = 7 Hz), 1.44 (d of t, 3 H, J = 7, 1 Hz).

With the collector at 0 °C, no 14 was found but the IR spectrum of the mixture contained a strong diethyl carbonate (1745 cm⁻¹) peak.

Methyl Fluoroformate from Carbonyl Fluoride. The COF₂ obtained from a mixture of phosgene (25.0 g, 0.25 mol), NaF (25.0 g, 0.60 mol), acetonitrile (7 mL), and sulfolane (22 mL) was passed into a collector maintained at -60 °C which contained methanol (5.40 g, 0.17 mol) and KF (11.0 g, 0.19 mol) in 15 mL of heptane. After 3 h, volatile products were vacuum evaporated into a -80 °C trap. Subsequent distillation then afforded the title product in 82% yield (10.8 g); bp 38-40 °C; IR (CCl₄) 1830 cm⁻¹ (s); ¹H NMR (CCl₄) δ 3.95 (s, 2 H).

When the collector temperature was at 0 °C, no fluoroformate was found. Instead, dimethyl carbonate (IR 1745 cm⁻¹) was obtained.

Attempted Synthesis of Diethylene Glycol Bisfluoroformate from Carbonyl Fluoride. Carbonyl fluoride obtained from the usual mixture of COCl₂ (35.8 g, 0.36 mol), NaF (37.0 g, 0.88 mol), sulfolane (37 g), and CH₃CN (20 mL) was bubbled into a collector (0 °C) containing KF (15.0 g, 0.28 mol), diethylene glycol (15.0 g, 0.1 mol), and diethyl ether (30 mL) for 3 h. Based on IR analysis of the slurry in the collector, the product (1750 cm⁻¹) probably was polymeric carbonate containing a trace of fluoroformate (1830 cm⁻¹).